REMARKS

The pending office action addresses claims 16-19, 21-25, and 29-33, claims 34-36 having been withdrawn as being directed to a non-elected invention. Currently, claims 16-19, 21-25, and 29-33 stand rejected. Applicant has amended claim 29 to correct a minor typographical error and to base the claim upon independent claim 16. Applicant respectfully requests reconsideration of the application, in view of the remarks below.

Claim Rejections Under 35 U.S.C. §112

In the present Office Action, the Examiner repeats his previous rejection of claims 16-33 under 35 U.S.C. §112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner objects to the term "representative genomic microarray" in claim 16, and the term "representative microarray" in claims 16, 17, 19, and 20, as being vague and indefinite.

Kindly note that the Applicant had already addressed these exact concerns and had responded in full to this same rejection in the November 26, 2003 response. In particular, Applicant amended claims 16, 17, and 19 to replace the phrase "representative" with the term "reference," which is fully supported on page 7, line 11 of the specification. Therefore, the present indefiniteness rejection is not applicable to currently pending claims 16-19, 21-25, and 29-33. Accordingly, Applicant respectfully requests withdrawal of this rejection.

Claim Rejections Under 35 U.S.C. §102 and §103

The Examiner continues to reject claims 16-19, 21-25, and 32 as being clearly anticipated by any one of Gingeras et al, Salama et al., or Chee et al. pursuant to 35 U.S.C. §102(a), (b), or (e). Claims 16-19 and 21-25 continue to be rejected as being anticipated by Eisen et al. pursuant to 35 U.S.C. §102(b). Finally, claims 29-31 continue to be rejected under 35 U.S.C. §103(a) as being unpatentable over any one of Gingeras et al., Salama et al., or Chee et al., in view of Berno (U.S. Patent No. 6,223,127), while claim 33 is again rejected under the same combination of references, and further in view of Applicant's admitted prior art. For the following reasons, Applicants respectfully request reconsideration and withdrawal of each of these rejections.

Applicant's Invention

Applicant's invention is directed to a method for identifying and analyzing polymorphic markers in a population by genotyping individuals of the population to a fabricated reference microarray, then assigning a binary digit of 0 or 1 corresponding to the hybridization ratio for each segment within that microarray, resulting in a bit string for each individual that is genotyped. Each bit has a unique position (corresponding to a selected segment of the microarray) within the bit string, and the relationship of these unique positions within the bit string are consistent for every bit string that is generated for any of the individuals hybridized to the reference microarray. To determine the relatedness of the bit strings and to identify unique bits among a plurality of bit strings, the commonality of bit values at corresponding positions along the bit strings is evaluated to ascertain which bits are present and which bits are absent for any of the bit strings being compared.

Independent claim 16 recites the steps of selecting a first and second individual from the population, hybridizing the genomic DNA of each of the individuals to a reference microarray, determining the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray, then converting the ratio to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual. Each of the strings has the same total number of bits and each bit has a unique position common to all the strings. Finally, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual.

By utilizing a binary conversion to represent hybridization patterns and an algorithm for analyzing the bit strings, Applicant's claimed invention enables the quick, simple determination of unique DNA sequence information for an entire genome. Once the bit strings are obtained, the commonality of bit values at corresponding positions along the bit strings is evaluated to ascertain which bits are present and which bits are absent for any of the bit strings being compared. In the case of a bacterial population, the bits can then be interrogated based on known genetic relationships of the strains or based upon other relationships, such as geographic origin. In this manner, array addresses that share common patterns of polymorphism among the populations of interest can quickly be identified. (*See,* page 3, lines 5-7 and 20-24).

The Prior Art

Turning now to the prior art, none of the references cited by the Examiner in his Office Action (or in Applicant's specification) discloses or teaches a method similar to that of the claimed invention. Gingeras et al., Salama et al., Chee et al., Eisen et al., and Berno are all directed to methods for the detection of polymorphisms in a population by hybridizing genomic DNA from an individual of a population to an array. Applicant admits that the problem of detecting polymorphisms in a population is well known. However, none of the cited references specifies the same methodology for determining this polymorphism that Applicant has disclosed and specifically claimed. Each of the Examiner's prior art rejections is addressed in detail below.

The Claimed Invention is Not Anticipated by the Cited References

For all of the following reasons, each of Gingeras et al., Salama et al., Chee et al., and Eisen et al. fail to clearly anticipate the claimed invention.

The Gingeras et al. Reference

According to the Examiner, "Gingeras et al teaches the genotyping of bacteria by nucleic acid molecular hybridization assays on microarrays . . . . for purposes of species indentification . . . . and utilizing fluorescent dyes." The Examiner further asserts on page 3 of the Office Action that the claimed methods are embraced by the disclosure in this reference. The Applicant respectfully disagrees.

As previously noted, methods for the detection of polymorphisms in a population by hybridizing genomic DNA from an individual of a population to an array are known in the art. However, none of the cited references specifies the same methodology for determining this polymorphism that Applicant has disclosed and specifically claimed. Here, Gingeras et al. discloses the use of high-density oligonucleotide arrays to perform genotypic analyses of the *Mycobacterium* species isolates with probes complementary to the *M. tuberculosis rpoB* gene sequence. The array serves as a generic genotyping chip that provides both specific nucleotide sequence as well as patterns of hybridization highly specific for each species. (*See*, page 436, 1st column). In order to analyze the results of hybridization patterns, Gingeras et al. teaches the use of cluster analysis. Specifically, four linkage methods (single, average, complete, and Ward's

minimum variance) were used to cluster the observations; the results of the cluster analysis were visualized as either dendrograms or as color grids. (*See,* page 443, FIG. 5 description and page 446, 2nd column).

Independent claim 16 requires the steps of selecting a first and second individual from the population, hybridizing the genomic DNA of each of the individuals to a reference microarray, determining the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray, then ***converting the ratio to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual.*** Each of the strings has the same total number of bits and each bit has a unique position common to all the strings. Finally, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual.

Gingeras et al. fails to disclose or suggest anywhere in his publication that the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the high-density oligonucleotide array can be converted to a ***binary digit of 0 or 1*** to produce a bit string of 0 or 1 bits for each individual, as required of independent claim 16. In fact, there is no mention whatsoever of a binary code or bit system for analyzing the hybridization patterns in Gingeras et al. Accordingly, Gingeras et al. cannot be said to clearly anticipate Applicant's claimed invention, as the reference fails to disclose or suggest each and every limitation of the claimed invention. For these reasons, Gingeras et al. is not a proper anticipatory reference. The Examiner is kindly asked to withdraw his 35 U.S.C. §102 rejection of the pending claims over Gingeras et al.

The Salama et al. Reference

According to the Examiner, "Salama et al teaches the detection of *Helicobacter pylori* by genome comparisons using nucleic acid molecular hybridization assays on microarrays . . . . using fluorescent dyes." The Examiner further asserts on page 3 of the Office Action that the claimed methods are embraced by the disclosure in this reference. The Applicant respectfully disagrees.

As previously noted, methods for the detection of polymorphisms in a population by hybridizing genomic DNA from an individual of a population to an array are known in the art.

However, none of the cited references specifies the same methodology for determining this polymorphism that Applicant has disclosed and specifically claimed. Independent claim 16 requires the steps of selecting a first and second individual from the population, hybridizing the genomic DNA of each of the individuals to a reference microarray, determining the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray, then ***converting the ratio to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual.*** Each of the strings has the same total number of bits and each bit has a unique position common to all the strings. Finally, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual.

Here, Salama et al. discloses the use of a binary score (gene present in a given strains = 1, absent = 0) for representing the hybridization results, then analyzing the data by average hierarchical clustering. (*See*, page 14670, 1st column and page 14672, FIG. 3 description). Although Salama et al. utilizes a binary code system to represent the presence or absence of genes, Salama et al. stops short of disclosing or suggesting that the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray can be converted to a binary digit of 0 or 1 to produce a ***bit string of 0 or 1 bits for each individual***, as required of independent claim 16. In Applicant's claimed invention, each of the strings has the same total number of bits and each bit has a unique position common to all the strings. Claim 16 also requires that the relatedness of the strings be determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual. In other words, Applicant's claimed invention involves a bit string to bit string comparison, to determine not just the ***presence*** of hybridization, but the ***location*** of the hybridization along the bit string. Salama et al. does not disclose or suggest any such step. Instead, Salama et al. appears to be interested only in the total number of hits (i.e., the total number of binary digits 1 or 0) for purposes of determining relatedness, and is not concerned with the location of where the hits occur. Salama et al. is clearly not interested in an individual-by-individual comparison, as is the Applicant.

Accordingly, Salama et al. cannot be said to clearly anticipate Applicant's claimed invention, as the reference fails to disclose or suggest each and every limitation of the claimed

invention. For these reasons, Salama et al. is not a proper anticipatory reference. The Examiner is kindly asked to withdraw his 35 U.S.C. §102 rejection of the pending claims over Salama et al.

The Chee et al. Reference

According to the Examiner, "Chee et al teaches analysis of genetic polymorphisms by nucleic acid molecular hybridization assays on arrays . . . . using fluorescent dyes." The Examiner further asserts on page 3 of the Office Action that the claimed methods are embraced by the disclosure in this reference. The Applicant respectfully disagrees.

As previously noted, methods for the detection of polymorphisms in a population by hybridizing genomic DNA from an individual of a population to an array are known in the art. However, none of the cited references specifies the same methodology for determining this polymorphism that Applicant has disclosed and specifically claimed. Independent claim 16 requires the steps of selecting a first and second individual from the population, hybridizing the genomic DNA of each of the individuals to a reference microarray, determining the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray, then ***converting the ratio to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual.*** Each of the strings has the same total number of bits and each bit has a unique position common to all the strings. Finally, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual.

Here, Chee et al. discloses the use of a mixture of pooled probes that are hybridized to a reference sequence, or reference array, and a binary code for representing the hybridization results. The results are analyzed using a tiling or trellis strategy, whereby the array of probes are aligned to detect complementarities. This produces an elaborate matrix representing hybridization patterns of the mixture of pooled probes to the reference array. This matrix enables Chee et al. to detect and identify all of the mutations at any given position in the sequence. (*See*, page 43, line 31 to page 44, line 35; page 46, lines 11-45; and page 52, lines 35-45). Although Chee et al. utilizes a binary code system to represent the presence or absence of hybridization, Chee et al. fails to disclose or suggest that the hybridization intensity ratio for

each of the hybridized and non-hybridized segments of the microarray can be converted to a binary digit of 0 or 1 to produce a ***bit string of 0 or 1 bits for each individual***, as required of independent claim 16. In Applicant's claimed invention, each of the strings has the same total number of bits and each bit has a unique position common to all the strings. In contrast, Chee et al. employs an analysis strategy in which

> [T]rellis strategy does not require that probes tile in increments of one or that the interrogation position positions occur in the same position each probe. In a variant of trellis tiling referred to as "loop" tiling, a nucleotide of interest in a target sequence is read by comparison of pooled probes, which each have a pooled interrogation position corresponding to the nucleotide of interest, but in which the spacing of the interrogation position in the probe differs from probe to probe.

Chee et al. is clearly not interested in an individual-by-individual comparison, as is the Applicant. Further, Chee et al. does not provide for an analysis method in which the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray can be converted to a binary digit of 0 or 1 to produce a ***bit string of 0 or 1 bits for each individual***, whereby each of the strings has the ***same total number of bits*** and each bit has a ***unique position common to all the strings***, as are required of the claimed invention.

Accordingly, Chee et al. cannot be said to clearly anticipate Applicant's claimed invention, as the reference fails to disclose or suggest each and every limitation of the claimed invention. For these reasons, Chee et al. is not a proper anticipatory reference. The Examiner is kindly asked to withdraw his 35 U.S.C. §102 rejection of the pending claims over Chee et al.

The Eisen et al. Reference

According to the Examiner, "Eisen et al teaches the genotyping of yeast by nucleic acid molecular hybridization assays on microarrays . . . . using fluorescent dyes." The Examiner further asserts on page 4 of the Office Action that "the claimed methods embrace the methods taught in Eisen et al." The Applicant respectfully disagrees.

As previously noted, methods for the detection of polymorphisms in a population by hybridizing genomic DNA from an individual of a population to an array are known in the art. However, none of the cited references specifies the same methodology for determining this

polymorphism that Applicant has disclosed and specifically claimed. Here, Eisen et al. discloses the use of DNA microarray hybridization to analyze gene expression in the budding yeast *Saccharomyces cerevisiae.* In order to analyze the results of the gene expression data, Eisen et al. teaches the use of pairwise average-linkage cluster analysis to produce a hierarchical tree, which can then be visualized graphically. (*See,* page 14863, 2nd column; and page 14864, 1st column to 2nd column). Independent claim 16 requires the steps of selecting a first and second individual from the population, hybridizing the genomic DNA of each of the individuals to a reference microarray, determining the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray, then ***converting the ratio to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual.*** Each of the strings has the same total number of bits and each bit has a unique position common to ***all the strings***. Finally, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual.

Eisen et al. fails to disclose or suggest anywhere in his publication that the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the DNA microarray can be converted to a ***binary digit of 0 or 1*** to produce a bit string of 0 or 1 bits for each individual, as required of independent claim 16. In fact, there is no mention whatsoever of a binary code or bit system for analyzing the hybridization patterns in Eisen et al. Accordingly, Eisen et al. cannot be said to clearly anticipate Applicant's claimed invention, as the reference fails to disclose or suggest each and every limitation of the claimed invention. For these reasons, Eisen et al. is not a proper anticipatory reference. The Examiner is kindly asked to withdraw his 35 U.S.C. §102 rejection of the pending claims over Eisen et al.

Conclusion

In conclusion, neither Gingeras et al., Salama et al., Chee et al., nor Eisen et al. anticipates the claimed invention because each of the references fails to disclose each and every limitation of the claimed invention. Although each of the cited references relates to the general concept of determining and analyzing hybridization patterns in a population, none of the cited references teaches the use of a binary code system for producing a bit string for each individual of the population being analyzed, whereby each of the bit strings has the same total number of bits and each bit has a unique position common to ***all the strings***. Failing to recite each and

every limitation of the claims, these references cannot clearly anticipate the claimed invention as asserted by the Examiner. The Examiner is asked to withdraw the rejections over Gingeras et al., Salama et al., Chee et al., and Eisen et al.

The Claimed Invention is Not Rendered Obvious by the Cited References

The Examiner rejects claims 29-31 as being unpatentable over any one of Gingeras et al., Salama et al., or Chee et al., in view of Berno. The Examiner also rejects claim 33 as being unpatentable over the same combination of references above, and further in view of Applicant's admitted state of the prior art. For all of the following reasons, the combination of either Gingeras et al., Salama et al., or Chee et al., in combination with Berno (U.S. Patent No. 6,223,127) either alone or with any prior art mentioned by Applicant, fails to render the claimed invention obvious.

Each of the Gingeras et al., Salama et al., and Chee et al. references fails to substantially disclose the claimed invention. Specifically, and as stated above, Gingeras et al. fails to disclose or suggest the conversion of hybridization ratios to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual hybridized to the microarray. Salama et al. fails to disclose the production of a bit string of 0 or 1 bits for each individual hybridized to the microarray, whereby each of the strings has the same total number of bits and each bit has a unique position common to ***all the strings***. Likewise, Chee et al. fails to disclose an analysis method in which the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray can be converted to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual, whereby each of the strings has the same total number of bits and each bit has a unique position common to ***all the strings***. None of these deficiencies in the cited references are overcome by their combination with the Berno patent.

In Applicant's invention, an algorithm is implemented which converts the hybridization ratio for each segment of the array into a binary digit of 0 or 1 to produce a bit string for each individual hybridized to the array. Each bit string generated has the same number of bits, and each bit has a unique position common to all the bit strings. To identify patterns of hybridization present in the population, the relatedness of the bit strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual, as required of the claimed invention.

In contrast, Berno discloses the use of cluster analysis to determine relatedness of the hybridized individuals in a population. As stated at col. 6, lines 10-55, cluster analysis is concerned with determining the closeness (i.e., the distances between segments) of hybridized segments and the number of groups of closely related segments that exist in the observed population. After all the distances are determined, an agglomerative hierarchical processing is implemented to group closely related (i.e., close in distance) genes so that a correlation or pattern, if any, can be ascertained. This process is not only significantly different but also significantly more complex than Applicant's method for determining relatedness. Applicant's claimed invention requires that entire bit strings be compared to one another, and the commonality and difference in value for each bit within the strings be determined. Specifically, the relatedness of the strings is determined by comparing the value of each bit within the bit string of the first individual to the value of each bit within the bit string of the second individual. By doing so, Applicant is able to provide a much simpler, more efficient process for observing the overall genetic profile of the individuals in a population. Since the entire genetic profile is observed, both mutations in the chromosomes of the populations of interest as well as the "noise" surrounding these markers (i.e., mutations in other chromosomes) can be ascertained. These features can be advantageous for evaluating the population in a phylogenetic context.

Moreover, Berno does not mention anywhere in the patent the use of a binary code system to represent hybridization intensity ratios, as is required of the claimed invention. Accordingly, the Applicant fails to see how the combination of any one of the Gingeras et al., Salama et al., or Chee et al. references with Berno, either alone or with any of the other references mentioned on page 5 of the Office Action, satisfies the claimed invention. Neither Gingeras et al., Salama et al., Chee et al., Berno, or any of the references mentioned by the Examiner on page 5 of the Office Action discloses a hybridization pattern analysis in which the hybridization intensity ratio for each of the hybridized and non-hybridized segments of the microarray is converted to a binary digit of 0 or 1 to produce a bit string of 0 or 1 bits for each individual, whereby each of the strings has the same total number of bits and each bit has a unique position common to ***all the strings***, as required of the claimed invention.

The cited references fail to teach or suggest all of the limitations of the claimed invention. For this reason, the presently pending claims are not anticipated or rendered obvious

by any of these references, nor would their combination satisfy any deficiencies that might exist. This is because the specific method of the claimed invention is not disclosed or taught in *any* of the cited references. Accordingly, the Examiner is respectfully requested to reconsider and to withdraw these rejections.

Finality of the Office Action

The Applicant respectfully requests withdrawal of the finality of this Office Action. As stated above, Applicant made amendments to the claims in the November 26, 2003 response which addressed in full the Examiner's indefiniteness rejections as well as the prior art rejections. However, the Examiner failed to consider these amendments in the present Office Action, repeating rejections which do not apply to the currently pending claims. Therefore, Applicant did not receive examination on the merits of the amendments previously made. For these reasons, Applicant submits that the finality of the Office Action is premature, and respectfully requests that Applicant be allowed an opportunity to have this response fully considered on its merits and acknowledged in the next correspondence.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

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